Analysis of mortality in neurofibromatosis 1 using U.S. death certificates

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Summary:

Although neurofibromatosis 1 (NF1) is a relatively common autosomal dominant condition, information about its effect on mortality is limited. We used Multiple-Cause Mortality Files, compiled from U.S. death certificates by the National Center for Health Statistics, for 1983 through1997. We identified 3,770 cases of presumed NF1 among 32,722,122 U.S. deaths, a frequency of 1 in 8,700, one-third to one-half the estimated prevalence. Mean and median ages at death for persons with NF1 were 54.4 and 59 years, respectively, compared with 70.1 and 74 years in the general population. Results of proportionate mortality ratio (PMR) analyses showed that persons with NF1 were 34 times more likely (PMR=34.3, 95% CI 30.8-38.0) to have a malignant connective or other soft tissue neoplasm listed on their death certificates than were persons without NF1. Overall, persons with NF1 were 1.2 times more likely than expected (PMR=1.21, 95%CI 1.14-1.28) to have a malignant neoplasm listed on their death certificates, but the PMR was 6.07 (95% CI 4.88-7.45) for persons who died at 10-19 years of age and 4.93 (95% CI 4.14-5.82) for those who died at 20-29 years of age. Similarly, vascular disease was recorded on death certificates of persons with NF1 more often than expected before 30 years of age (PMR=3.26, 95% CI 1.31-6.71 at age < 10 years; PMR=2.68, 95% CI 1.38-4.68 at age 10-19 years; PMR=2.25, 95% CI 1.46-3.32 at 20-29 years), but not in older persons. This study supports previous findings of decreased life expectancy for persons with NF1 and, within the limitations of death certificates, provides population-based data about NF1 morbidity and mortality useful to clinicians caring for patients with NF1.

Introduction:

Neurofibromatosis 1 (NF1 [MIM 162200]) is a relatively common autosomal dominant disorder, with a frequency of 1 in 3,000-4,000 persons (Poyhonen et al. 2000; Rasmussen and Friedman 2000). Cardinal features include multiple café-au-lait spots, benign neurofibromas, and Lisch nodules of the iris; learning disabilities, mild shortness of stature, and skeletal abnormalities are common. An increased risk for malignancy has also been observed in NF1 and may be related to the proposed tumor suppressor role of the *NF1* gene (Shen et al. 1996).

Despite the high prevalence of NF1, information about its effect on mortality is limited. Sørensen and associates (1986) followed a cohort of 212 patients with NF1 identified 42 years earlier in Denmark. Because probands had been identified through hospitals and might, therefore, be more severely affected, the authors analyzed data on both probands and affected relatives. Survival of people with NF1 was significantly lower than that of the general population, and more so in probands than in affected relatives. Malignant neoplasms were significantly increased, primarily in probands (Sørensen et al. 1986; Neerup Jensen et al. 1998).

A 12-year follow-up of 70 adult NF1 patients (Zöller et al. 1995) found a decrease in life expectancy of about 15 years. Malignancy was the cause of death for more than half the patients, and hypertension was significantly associated with mortality. A third study used data on 605 deaths from Japanese vital statistics for 1968-1992 in which "neurofibromatosis" was listed as the underlying cause of death. The mean age at death in this study was 43 years (Imaizumi 1995). However, the authors did not distinguish between persons with NF1 and neurofibromatosis 2 (NF2), and no data were available in this study on causes of death other than neurofibromatosis. In addition, because only cases

in which neurofibromatosis was listed as the underlying cause of death were included, neurofibromatosis was believed to be underascertained in this population (Imaizumi 1995).

In the present investigation, we used data from U.S. death certificates to study mortality among NF1-associated deaths. Our population-based study includes data on over 3,700 deaths of people with NF1 for 1983-1997. We used these data to examine mean and median ages of death and the most common conditions associated with death in persons with NF1 compared with the general U.S. population.

Methods:

We used the Multiple-Cause Mortality Files (MCMF), compiled from U.S. death certificates by the National Center for Health Statistics of the Centers for Disease Control and Prevention. MCMF include demographic and geographic information and *International Classification of Disease, Ninth Revision* (ICD9), codes for the underlying cause of death and up to 20 conditions listed on the death certificate as "other significant conditions" (Israel et al. 1986) The ICD9 coding system has been used for mortality statistics since 1979; however, because of incomplete collection of death certificates for 1981 and 1982, NCHS partially replicated data for these years (Israel et al. 1986). We were concerned about the effect of this case duplication on our small subset of cases with neurofibromatosis, so we limited our study to 1983-1997.

The codes in the MCMF are in two formats: entity axis and record axis. The entity axis format provides a separate code for each disease listed, whether it is an underlying cause of death or a contributory condition. The record axis format uses linkage rules to combine some listings of conditions

on the death certificates. We selected all cases listing the ICD9 code for "neurofibromatosis (von Recklinghausen's disease)" (237.7) in the record axis. This code may also include cases of the much less common but generally more severe condition NF2. We therefore excluded cases with the codes for "sensorineural deafness" (389.1), "benign neoplasms of cranial nerves" (225.1), "benign neoplasms of cerebral meninges"(225.2) and "benign neoplasms of spinal meninges" (225.4) as probable NF2. For the remaining cases, we determined mean and median ages at death to approximate the survival of persons with NF1 overall and by sex and race. Race is classified as "white", "black" or "other" in the Multiple-Cause Mortality Files; however, given the small number of cases of other races, we grouped race into two categories, "white" and "other". Because the distribution of age at death was skewed, a logarithmic transformation was applied to these data to obtain the geometric mean age at death and the associated 95% confidence intervals (CIs). We used the nonparametric median scores method to test the differences of median age at death. Version 8.0 of the SAS program (SAS Institute, Cary, NC) was used for all analyses.

To investigate the relation of NF1-associated deaths to other medical conditions, we calculated the proportionate mortality ratio (PMR) for deaths of persons with NF1 for several conditions. The PMR was calculated as the observed number of deaths with a specific condition among deaths of persons with NF1 divided by the expected number of deaths with the specific condition. The expected number of deaths associated with a particular condition was calculated from the proportion of death certificates in the U.S. population listing that condition during 1983-1997, adjusted for decedent's age, sex, race and death-cohort (Hennekens 1987). Because the complete file containing over 32 million deaths was too large for convenient computation, we used a randomly selected subset containing 25%

of U.S. deaths during 1983-1997 to calculate the expected number of deaths for each condition. We calculated 95% CIs by assuming the number of deaths associated with NF1 and another medical condition was distributed as a Poisson variable (Ahlbom 1993). PMR enables determination of whether a specific medical condition is more or less likely in deaths in which NF1 is listed on the death certificate, compared with all deaths. If the medical condition is more likely in NF1 cases, the PMR will be greater than 1; if the medical condition is less likely, the PMR will be less than 1. We selected 90 conditions for PMR analysis on the basis of their frequency as causes of death in the general population or because of their known association with NF1 morbidity or mortality (Sørensen et al. 1986; Zöller et al. 1995; McGaughran et al. 1999). For selected conditions, we also evaluated PMRs by age group at death (< 10, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, or ≥ 70 years). For this study, we defined vascular disease as hypertensive disease (ICD9 401-405), cerebrovascular disease (ICD9 430-438), or a disease of the arteries or arterioles (ICD9 440-449). This range includes renal artery stenosis (ICD9 440.1), but does not include heart disease which we considered separately. We defined "heart disease (adult)" as ischemic heart disease (ICD9 410-414), diseases of the pulmonary circulation (ICD9 415-417), and other forms of heart disease (ICD9 420-429).

Results:

We identified 3,829 cases with the code for neurofibromatosis listed on the death certificate. We excluded 59 cases as probable NF2: 24 cases with "benign neoplasms of cranial nerves" (225.1), 32 cases with "benign neoplasms of cerebral meninges"(225.2) and 3 cases with both of these codes. No cases had neurofibromatosis and "sensorineural deafness" (389.1) or "benign neoplasms of spinal

meninges" (225.4) coded. The mean and median ages at death of the excluded case-decendents was 40.1 and 32 years, respectively.

Among 32,722,122 deaths, 3,770 presumed NF1 deaths remained, a frequency of 1 NF1-associated death per 8,700 deaths in the United States. The mean age at death of persons with NF1 was 15.7 years lower than the mean age at death in the general population (Table 1). Although the mean age at death of females with NF1 was over 3 years higher than that of males with NF1, the difference between the mean ages at death of persons with NF1 and of the U.S. general population was greater for females. The mean age at death of persons with NF1 of other races was earlier than for white persons, but the difference between the mean ages at death of persons with NF1 and of the general population was greater for whites than for those of other races. The difference between mean ages at death of persons with NF1 and the general population increased over the three 5-year periods studied.

The median age at death of persons with NF1 was 59 years, whereas the median age at death of the U.S. population was 74 years (Figure 1). The median age at death of females with NF1 was decreased more than that of males with NF1, compared with the general population. The median age at death of persons of other races with NF1 decreased more than that of whites with NF1, compared with the general population. The difference between median ages at death of NF1 cases and of the general population increased over the three 5-year time periods studied.

Because we wondered if the effect of NF1 mortality was restricted to younger patients, we also evaluated the mean and median age at death of persons dying at age 40 years or older. The mean age at death of persons with NF1 who survived 40 years or more was 65.6 years, whereas the mean age at

death for this subset of the U.S. population was 74.5. The median age at death of persons with NF1 dying at age 40 years or older was 67 years, compared with 76 years for the U.S. population.

Malignant neoplasms (all), vascular disease, cerebrovascular disease (a component of vascular disease), scoliosis, epilepsy and mental retardation were reported more frequently than expected on death certificates of people with NF1 (Table 2). Diabetes mellitus and suicide were reported much less often than expected on death certificates of persons with NF1, and heart disease (adult) and diseases of the arteries and arterioles were reported slightly less often than expected.

Malignant neoplasms of connective and other soft tissue were reported 34 times more frequently than expected, and neoplasms of the brain were reported 5.5 times more frequently than expected among NF1-associated deaths (Table 3). Other neoplasms were less likely to be listed on the death certificates of persons with NF1 than on those of the general population, and this decrease reached statistical significance for malignant neoplasms of the lymphatic/hematopoietic system, breast (in females), trachea/bronchus/lung, pancreas, large bowel, prostate, uterine cervix, and skin. The PMR for all malignant neoplasms excluding those of connective and other soft tissue and brain was significantly less than 1.

Malignant neoplasms as a group occurred more frequently than expected among persons less than 39 years of age who had NF1 (Table 4). When connective and other soft tissue and brain neoplasms were excluded from malignant neoplasms, the PMR was elevated for persons aged less than 20 years The PMR for myeloid leukemia was substantially increased for children aged less than 10 years, but malignant neoplasms of the lymphatic and hematopoietic system as a group were reported significantly less often than expected among persons aged 20-49 years who had NF1. Malignant

neoplasms of connective and other soft tissue occurred much more frequently than expected among persons with NF1 at all ages, and the PMR was over 50 for persons who died at age 20-39. Malignant neoplasms of the brain were reported more often on death certificates of persons with NF1 at all ages below 70 years.

Vascular disease was reported more often than expected among persons with NF1 aged less than 29 years, but not in those who were older. The pattern was similar for cerebrovascular disease considered alone, but the PMR for hypertensive disease increased only among persons with NF1 who were 20-29 years old, and the PMR for diseases of the arteries and arterioles decreased among persons over age 60 who had NF1.

Discussion:

Our finding that survival, as estimated by mean and median age of death, is about 15 years less than expected in persons with NF1 is consistent with the results of previously reported smaller studies. Zöller et al. (1995) followed 70 adult NF1 patients for 12 years and estimated that the mean length of life for persons with NF1 was about 15 years shorter than expected. Inclusion of NF1 cases presenting in childhood probably would have lowered the life expectancy even further (Zöller et al. 1995). The study by Imaizumi (1995) found a mean age at neurofibromatosis-associated death of 43 years in a Japanese population, much lower than that seen in our study. However, their study only included cases for which "neurofibromatosis" was listed as the underlying cause of death, whereas our study included all cases mentioning neurofibromatosis anywhere on the death certificate and excluded cases more likely to be NF2 than NF1. Neurofibromatosis was likely to be significantly

underascertained in their study, resulting in a larger proportion of severe cases than ours. Thus, our study is more likely to be representative of all people with NF1.

Examination of mean and median ages at death suggests that survival of females with NF1 is more severely affected than that of males, in comparison with population expectations. Results from the study by Zöller et al. (1995) also suggested that women with NF1 may be more severely affected than men. In the study by Sørensen et al. (1986), female probands had the lowest survival rate, but survival of female relatives with neurofibromatosis was only slightly less than that of the general population. Another possible explanation is that NF1 may be more likely to be diagnosed earlier in females, and thus NF1 may be listed more often on death certificates of females with NF1 who die earlier. In support of this, the frequency of deaths for which NF1 was listed on the death certificate is somewhat greater among females than among males (1 in 8343 deaths for females, compared with 1 in 9019 for males). Further study is needed to determine whether NF1 affects survival more in females than in males.

Evaluating the effect of race on NF1 mortality is more difficult. On the basis of the difference between the mean ages at death of persons with NF1 and of the general population, whites may be more severely affected than other races; however, the opposite is seen among median ages at death. On the basis of evaluation of mean and median ages at death by time period, the effect of NF1 on mortality appears to be increasing. However, these results could be secondary to earlier ascertainment of cases with NF1 in more recent years than previously.

The highest PMR in our study was for malignant neoplasms of connective and other soft tissue, a category that includes malignant peripheral nerve sheath tumors. These results are consistent with the

rarity of these tumors in the general population, their poor prognosis, and their greatly increased frequency among persons with NF1 (Woodruff 1999; King et al. 2000). This type of tumor was a major cause of mortality in previous studies as well. In the study by Zöller et al. (1995), three of the 22 patients who died during the period of observation had soft tissue sarcomas.

We also found a significantly increased PMR for malignant neoplasms of the brain. A significant excess of brain tumors was also found in the study by Sørensen et al. (1986). Of 212 patients with malignant tumors, 21 (10%) had tumors of the central nervous system. However, some of these persons may have had NF2 (Zöller et al. 1995). A high proportion of brain tumors was also seen in a follow-up study of NF1 patients previously evaluated in a neurofibromatosis clinic (Airewele et al. 2001).

Malignant neoplasms are a major cause of death in people with NF1: about 55% of the cohort followed by Zöller et al. (1995) died from a malignancy, a rate higher than expected when compared with data from a cancer registry (Zöller et al. 1995). Our study also shows an increased PMR for malignancy for persons with NF1, but the excess was seen only among people who died at less than 40 years of age. This increased PMR appears to be due primarily to brain tumors and malignant neoplasms of connective and other soft tissue. When these types of cancer are excluded, the PMR for malignant neoplasms among deaths of persons with NF1 is lower than expected (PMR=0.69, 95% CI 0.64-0.75).

The PMR for myeloid leukemia was significantly elevated among death certificates of children with NF1 who died at less than 10 years of age. This observation is consistent with the known relation between juvenile chronic myelogenous leukemia and NF1 and the age at which this malignancy occurs

(typically less than 4 years at time of diagnosis) (Hess et al. 1996). Myeloid leukemia was no more frequent than expected in deaths among persons with NF1 at other ages.

A number of reports have described life-threatening or fatal vascular abnormalities in young patients with NF1. The most frequently described manifestations are severe hypertension, usually associated with renal artery stenosis, and cerebrovascular disease associated with moyamoya disease (Sobata et al. 1988; Muhonen et al. 1991; Hattori et al. 1998; Kwong and Wong 1999; Fossali et al. 2000). Zöller and colleagues (1995) found that hypertension was significantly associated with NF1 mortality in a series of 70 adult patients followed for 12 years. PMR for vascular disease was slightly higher than expected among deaths of persons with NF1 than among others, and this effect was especially prominent among persons who died at less than 29 years of age. Most of this increase in the PMR appears to be related to cerebrovascular disease rather than to hypertensive disease or other diseases of the arteries or arterioles.

Based on our evaluation of PMRs by age group, the impact of NF1 on mortality from vascular disease and malignancy appears to be focused on persons under age 40 years. However, even among persons with NF1 surviving to age 40, the mean and median ages at death are decreased by about nine years when compared to the U.S. population. This is in contrast to the 15-year decrease observed among all persons with NF1, and suggests that NF1 affects mortality even at older ages, although less than in earlier years.

This study has several important strengths. The use of MCMF allows a population-based analysis and comparison of data to the general population. The study is based on data from recent years, and data are available on 3,770 deaths of people with NF1, many more than all previous studies

combined. In addition, our study provides data on deaths at all ages, whereas most previous studies have been limited to deaths among adults.

Our study also has several important limitations. First, the data are based on death certificates, which previous studies have demonstrated to be both incomplete and, in some instances, inaccurate (Sirken et al. 1987; Lloyd-Jones et al. 1998) . The low PMR observed for suicide may be related to this issue; physicians completing death certificates on persons who died of suicide may be less likely to also list NF1. Second, ICD9 does not allow for distinction between NF1 and NF2. We excluded cases coded as neurofibromatosis that had features more characteristic of NF2 than of NF1, but some cases of NF2 probably have been included and some cases of NF1 may have been excluded from our study. NF1 cases appear to be underascertained in our study population. The proportion of death certificates listing neurofibromatosis is one-third to one-half the estimated population prevalence of NF1 (Poyhonen et al. 2000; Rasmussen and Friedman 2000). This underascertainment could introduce a critical bias if NF1 is more likely to be listed on the death certificates of persons with more severe disease or with complications that are well known to be associated with NF1.

In addition, the ICD9 coding system used for mortality statistics is often not specific enough to provide all the information needed for a study of this kind. This limited our analysis of benign tumors; for example, plexiform neurofibromas are coded under the code 215 (other benign neoplasm of connective and other soft tissue), but this code may also include other tumors, such as cutaneous neurofibromas, making analysis of this category impossible.

Another limitation is that our analyses of PMR used multiple comparisons, increasing the likelihood of demonstrating a statistically significant association when one may not exist (Rothman and

Greenland 1998). We initially selected 90 codes on which to perform PMR analyses and subsequently performed additional analyses on eight age groups. However, the codes were not selected randomly, but instead focused on known associations with NF1 and common causes of death in the general population. It is reassuring that our PMR analyses generally confirm previous well-recognized associations in NF1.

Without information about the number of persons with NF1 living in the United States during each year of the study, we cannot be certain that our PMRs actually reflect altered disease-related survival among persons with NF1. A PMR could be lower than expected if competing causes of mortality eliminated patients who would have developed a particular disease if they had lived long enough (Kupper et al. 1978; Hennekens 1987). However, such effects would have to be differential to affect the PMR; that is, for competing causes of mortality to produce a reduced PMR, persons with NF1 who would have died from one condition later in life would have to die from something else earlier, and persons with NF1 who are unlikely to die from that condition later in life would rarely die from these alternative causes earlier.

Since the PMR is a ratio, an increase in one cause of death results in a decrease in all other causes (Decoufle et al. 1980). The PMR could, therefore, be reduced if the rate of a particular condition is unchanged but the death rate associated with other medical conditions is greatly increased, or vice versa. The PMR calculation is based on the assumption that the overall rate of death from all causes is the same in the two groups being compared. This is unlikely to be true in the comparison between people with and without NF1. To the extent that death from all causes is more likely among people with NF1, the PMRs we calculated will underestimate the true cause-specific standardized

mortality ratio (Roman et al. 1984). An alternative method of analyzing mortality with death certificate data that is not subject to this same limitation is the standardized mortality odds ratio (SMOR) (Miettinen and Wang 1981). We also performed SMOR analyses on these data, and the results were similar to those reported here for the PMR (data not shown).

In conclusion, based on our analysis using data from U.S. death certificates, persons with NF1 appear to have a decreased life expectancy of about 15 years in comparison to the general population. However, since NF1 may have been significantly underascertained in our study population, our analysis may overestimate the difference in life expectancy between persons with NF1 and the general population. Certain kinds of malignancy (especially brain tumors and malignant neoplasms of connective and other soft tissues) appear to occur more frequently than expected in people who die with NF1, but other kinds of cancer do not. Such malignancies and vascular disease, especially cerebrovascular disease, both appear to contribute disproportionately to mortality in children and young adults with NF1.

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Electronic-Database Information:

Accession numbers and the URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for NF1 [MIM 162200])

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Table 1
Geometric Mean Age at Death of Persons with NF1
and of the U.S. General Population, 1983-1997

Category	Number of Deaths	Mean Age (Yrs.) at Death of Persons with NF1	Mean Age (Yrs.) at Death of US Population	Difference Between Means	95% CI
All	3,770	54.4	70.1	15.7	15.0-16.3
Males	1,874	52.7	66.4	13.7	12.8-14.6
Females	1,896	56.1	74.0	17.9	17.1-18.7
Whites	3,150	55.4	71.5	16.1	15.4-16.7
Other Races	620	49.6	61.3	11.7	9.7-13.4
1983-1987	1,183	54.9	69.2	14.3	13.2-15.4
1988-1992	1,247	53.9	69.8	15.9	14.8-17.0
1993-1997	1,340	54.5	71.0	16.5	15.5-17.6

Table 2
Proportionate Mortality Ratios (PMRs) for Selected Medical Conditions of NF1-Associated Deaths, 1983-1997

Condition	ICD-9 Code	Observed Cases	Expected Cases	PMR	95% CI
Malignant neoplasms (all)	140-208	1170	965	1.21	1.14-1.28
Heart disease (adult)	410-414, 415-417, 420-429	1365	1571	0.87	0.82-0.92
Heart disease (congenital)	745-747	19	19.9	0.95	0.57-1.49
Vascular disease	401-405, 430-438, 440-447	658	597	1.10	1.02-1.19
Hypertensive disease	401-405	244	219	1.11	0.98-1.26
Cerebrovascular disease	430-438	398	327	1.22	1.10-1.34
Diseases of arteries and arterioles	440-447	123	157	0.78	0.65-0.93
Diabetes mellitus	250	64	239	0.27	0.21-0.34
Curvature of spine (Includes scoliosis/kyphosis)	737	66	2.72	24.3	18.8-30.9
Epilepsy	345	35	10.3	3.40	2.37-4.73
Mental retardation	317-319	43	9.00	4.78	3.46-6.44
Suicide	E950-E959	7	137	0.05	0.02-0.11

Table 3
Proportionate Mortality Ratios (PMRs) for Selected Malignant Neoplasms of NF1-Associated Deaths , 1983-1997

Type of Malignant Neoplasm	ICD-9 Code	Observed Cases	Expected Cases	PMR	95% CI
Connective and other soft tissue	171.0-171.9	353	10.3	34.3	30.8-38.0
Brain	191.0-191.9	181	32.8	5.52	4.74-6.38
Lymphatic/Hematopoietic system	200-208	69	113	0.61	0.48-0.77
Myeloid leukemia	205.0-205.9	20	20.9	0.96	0.58-1.48
Female breast	174.0-174.9	79	120	0.66	0.52-0.82
Trachea/Bronchus/Lung	162.0-162.9	132	236	0.56	0.47-0.66
Stomach	151.0-151.9	22	23.5	0.94	0.59-1.42
Liver and intrahepatic bile ducts	155.0-155.9	11	16.1	0.68	0.34-1.22
Pancreas	157.0-157.9	24	39.4	0.61	0.39-0.91
Colon, rectum, rectosigmoid junction and anus	153.0-154.9	38	94.6	0.40	0.28-0.55
Ovary	183.0	21	28.8	0.73	0.45-1.11
Prostate	185.0-185.9	16	42.6	0.38	0.21-0.61
Cervix uteri	180.0-180.9	4	18.7	0.21	0.06-0.55
Body of uterus and of uterus, part unspecified	179.0-179.9, 182.0-182.9	11	12.0	0.92	0.46-1.64
Skin (malignant melanoma)	172.0-173.9	12	23.2	0.52	0.27-0.90

All neoplasms, excluding connective and soft tissue and brain	140-208 excluding 171 and 191	638	922	0.69	0.64-0.75

Table 4

Proportionate Mortality Ratios (PMRs) for Selected Medical Conditions of NF1-Associated Deaths by Age Group, 1983-1997

	Age Group (Years) and 95% CIs							
Condition	< 10	10-19	20-29	30-39	40-49	50-59	60-69	≥ 70
Malignant neoplasms (all)	3.94 (2.60-5.73)	6.08 (4.88-7.45)	4.93 (4.14-5.82)	2.13 (1.83-2.47)	1.18 (1.00-1.37)	0.89 (0.76-1.05)	0.77 (0.67-0.89)	0.84 (0.74-0.96)
Malignant neoplasms excluding cases with connective and soft tissue and brain	3.15 (1.76-5.19)	1.76 (1.07-2.71)	1.27 (0.86-1.82)	0.55 (0.39-0.75)	0.58 (0.45-0.73)	0.67 (0.55-0.81)	0.59 (0.50-0.69)	0.75 (0.65-0.87)
Malignant neoplasms of connective and soft tissue	16.1 (5.24-37.6)	38.3 (27.8-51.7)	52.4 (41.8-65.2)	50.2 (40.3-62.0)	31.5 (23.5-41.3)	22.1 (14.7-31.9)	22.9 (15.6-32.3)	18.3 (11.6-27.4)
Malignant neoplasm of brain	3.94 (1.58-8.10)	11.4 (7.53-16.4)	9.32 (6.14-13.5)	7.99 (5.86-10.7)	5.73 (3.96-8.00)	2.99 (1.68-4.94)	3.44 (2.07-5.38)	1.47 (0.48-3.42)
Malignant neoplasms of lymphatic/hematopoietic system	2.35 (0.94-4.84)	0.28 (0.03-1.01)	0.20 (0.02-0.72)	0.07 (0.002-0.39)	0.43 (0.16-0.93)	0.64 (0.29-1.22)	0.74 (0.42-1.20)	0.91 (0.59-1.33)
Myeloid leukemia	10.4 (3.38-24.3)	1.26 (0.15-4.54)	0.00 (0.00-1.51)	0.27 (0.007-1.51)	0.64 (0.08-2.32)	0.00 (0.00-1.51)	1.20 (0.33-3.08)	1.60 (0.59-3.48)
Vascular disease	3.26 (1.31-6.71)	2.68 (1.38-4.68)	2.25 (1.46-3.32)	1.04 (0.70-1.50)	1.02 (0.75-1.35)	1.12 (0.87-1.42)	1.19 (1.00-1.40)	1.01 (0.90-1.12)
Hypertensive disease	0.00 (0.00-28.4)	6.32 (0.76-22.6)	3.27 (1.32-6.74)	0.32 (0.07-0.93)	1.07 (0.68-1.59)	1.01 (0.69-1.43)	1.19 (0.91-1.53)	1.13 (0.93-1.35)
Cerebrovascular disease	3.63 (1.46-7.47)	2.76 (1.32-5.07)	2.09 (1.19-3.39)	1.20 (0.74-1.83)	0.85 (0.53-1.30)	1.54 (1.12-2.07)	1.46 (1.16-1.81)	1.06 (0.92-1.22)

Diseases of arteries and arterioles	0.00 (0.00-26.3)	0.00 (0.00-5.51)	2.48 (0.80-5.78)	1.15 (0.37-2.69)	1.42 (0.71-2.55)	0.62 (0.27-1.23)	0.57 (0.34-0.90)	0.78 (0.61-0.97)

Figure 1

Median ages at death (in box) and 5th, 25th, 75th and 95th percentiles of persons with NF1 and of the U.S. general population for all cases and by sex, race, and time period